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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,043	03/01/2006	Martin Fussenegger	2006-0153A	6327

513 7590 04/29/2008

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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,043	FUSSENEGGER ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *10-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-01-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of claims. Claims 1-27 are pending. Applicants' election of Group I, drawn to claims 1-9, in the reply filed on 01-22-2008 is acknowledged. Applicants' election of the following species is acknowledged: (1) binding changed in response to compounds being gaseous as recited in claim 3. The examiner has withdrawn the species restriction requirement in relation to compounds being gaseous or liquid as recited in claims 3 and 4, respectively. The search and examination of both species together will not impose a serious burden in the examiner. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-9 are currently under examination to which the following grounds of rejection are applicable.

Nucleotides and/or amino acid sequences. Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

1. This application contains sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821. (a)(1) and (a)(2) which states". However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth. Specifically the application fails to comply with CFR 1.821 (d), which states:

(d) Where the description or claims of a patent application discusses a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. At page 8, the specification teaches the nucleotide sequences used as primers (e.g., forward and reverse primers) to PCR the responsive promoter containing the AlcR-specific operator site (OP site) derived from *Aspergillus nidulans* P_{alcA} comprising unbranched sequences of more than 10 nucleotides , all of which lack sequence identifiers. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing". (see MPEP 2422.03). Applicant is required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures by amending the specification to include the appropriate SEQ ID NOS following each recitation of an amino acid sequence or nucleotide sequence meeting the criteria of 37 CFR 1.821(a).

Moreover, for compliance with the sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing". (see MPEP 2422.03). Additionally, Applicants must submit:

2. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(c).

3. A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

To be fully responsible for restriction, Applicant is required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

Claim Objection

Claims 1, 3 and 4 are objected to because of the following informalities: the phrase "OP operator-containing promoters" as recited in claim 1, subpart a, is not consistent with the phrase "OP-containing promoters", as recited in claims 3 and , potentially creating problems in claim interpretation. The use of terms should be consistent throughout the claims. Appropriate correction is required.

Claims 1 is objected to because of the following informalities: acronyms such RTF or OP should be enclosed in parenthesis as a comment after the full spelling of the term in the claim. Applicant may wish to consider amending the claims to read ---operator-containing promoter (OP) --- at line 2 of the claim for clarity, for example.

Specification Objection

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Specifically, the specification discloses at page 2, paragraph [005], the Internet address for the White et al., publication.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1 and dependent claims 2-9 are rejected under 35 U.S.C. § 101 because the claimed invention is drawn to non-statutory subject matter.

The preamble of the claim 1 recites "A mammalian cell comprising:...". Thus claim 1 reads broadly on any mammalian cell comprising a promoter with operator sites (e.g., response elements) that may be activated in response to a transcription factor which itself is induced by any liquid or gas compound. Transcription factors binding cognate response elements in promoter sequences of a gene to regulate transcriptional activation of said genes in mammalian cells are commonly used regulatory mechanisms well known in the art for transcriptional control throughout eukaryotic genes. For example, claim 1 reads on mammalian cells comprising promoters with hormone binding domains regulated by endocrine factors reaching a mammalian target cell in blood fluid resulting in hormone-activated gene expression. The mammalian cell broadly encompassed by claim 1 is not isolated or purified, is a product of nature that is not statutory subject matter because it fails to show the "hand of man" in their construction and because they read on non-isolated mammalian cells. Amending claim 1 to recite "An isolated mammalian cell..." would be remedial.

Claim Rejections - 35 USC § 112- Second paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 1, subpart a. recites "at the cultivation temperature" . However, there is not a proper antecedent bases in the preamble of claim 1 for the phrase "at the cultivation temperature". As such, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 112, first paragraph

The instant claims are broadly drawn to mammalian cells comprising transcription factors that modulate gene transcription in response to a compound e.g., liquid or gaseous, by regulating promoter sequences in said genes (e.g., operator containing promoters). As such, the instant claims are enabling. In fact, the claims read on art as shown in the claim rejections under - 35 USC § 102 and - 35 USC § 103 in the paragraphs below . The instant issue of enablement is based on the fact the instant claims embrace a subgenus of promoter domains containing specific operator sites derived from those found in the *A. nidulans* P_{alcA} promoter containing modified nucleotides. To the extent that the claims read on promoter domains containing specific operator sites derived from those found in the A. nidulans P_{alcA} promoter containing modified nucleotides which are activated by *A. nidulans*-induced AlcR transcription factor, the following rejections apply.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9, as best understood, are readable on a genus of nucleic acid regions of a promoter gene, able to specifically bind a RTF which modulates the transcription of said promoter in response to a gaseous or liquid compound, wherein the genus of nucleic acids of a promoter gene is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that one skilled in the art could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification teaches at page 5, the *Aspergillus nidulans* AlcR protein, which binds to the corresponding operator sequence as disclosed in GenBank accession No. S47331, nucleotides 30-308, in response to acetaldehyde (GenBank Accession No. S47331). The specification exemplifies the construction of plasmid pWW192 comprising a PCR-amplified promoter using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3') from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector. Moreover, the specification teaches transfection of CHO-K1 cells with plasmid pWW192 and induction of gene reporter activity in a dose dependent manner with increasing concentrations of acetaldehyde from tobacco smoke (p. 8, paragraphs [043]-[046]. Though the specification contemplates other promoter domains containing specific operator sites derived from those found in the A. nidulans P_{alcA} promoter containing modified nucleotides (p. 5,

paragraph [027]) activated by *A. nidulans*-induced AlcR transcription factor, there is no structure/function relationship taught at all for claimed genus of promoter regions of a *A. nidulans* P_{alcA} gene, much less fragments of any promoter gene. There is no teaching of how many nucleotides may be mutated and/or deleted in the PCR-amplified promoter from a P_{AlcA} containing vector that may affect AlcR-mediated transactivation in the presence of acetaldehyde. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, as one of skill in the art cannot envision all the promoter regions of a *A. nidulans* P_{alcA} gene able to exhibit AlcR-mediated transactivations induced by acetaldehyde.

At the time the invention was made, it was well known in the art that patterns of single mutations in promoters are critical to their structure/function relationship, particularly, various sites or regions directly involved in promoter response elements, TAT elements and initiator elements necessary for binding of trans-activators and RNA polymerase, which regulates transcriptional activation (Romanos et al., 1992, Yeast, pp. 423-488; p. 431, col. 2). The skilled artisan understands that one nucleotide change in a DNA molecule could result in the loss of its biological activity as demonstrated, for example, in the yeast his3 promoter region wherein individual mutations of the regulatory TATA elements, TATAAA, abrogate the functional activity of the promoter, likely by preventing binding of sequence specific DNA-binding proteins (Chen et al., 1988, Proc Natl Acad Sci pp. 2691–2695, Abstract). Since, the relationship between the a *A. nidulans* P_{alcA} gene and transcriptional factors modulating its activity is not well understood and is not predictable, the disclosure provided is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of

skill in the art cannot envision a genus of promoters domains of *A. nidulans* P_{alcA} gene transactivated by the A. *nidulans* AlcR responsive transcription factor. Thus, it is not possible from reading the examples to envision what types of mutations have been introduced, how many mutations have been introduced in each promoter region of the *A. nidulans* P_{alcA} gene so as to exhibit *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde.

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., P_{alcA} nucleotide sequence), specific features and functional attributes (e.g *A. nidulans* AlcR-mediated transactivations in the presence of acetaldehyde) that would distinguish different members of the claimed genus. In the instant case, no other characteristic in addition to the functional discussed above are disclosed. Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera form each other. Although sufficient description is given for the PCR-amplified promoter from a *A. nidulans* P_{AlcA} using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as primers, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of nucleic acid regions of a promoter of *A. nidulans* P_{alcA} gene, exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde, much less fragments of any promoter exhibiting responsive transcription factor-mediated transactivation in the presence of any compound being gaseous. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a PCR-amplified promoter from a *A. nidulans* P_{AlcA} using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as forward and reverse primers,

the specification does not provide an enabling disclosure for a genus promoter regions of a *A. nidulans* P_{AlcA} gene operably linked to operator sites specific exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde, much less a genus promoter regions of any promoter exhibiting responsive transcription factor-mediated transactivation in the presence of any compound being gaseous.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a genus of unspecified promoter regions a genus of nucleic acid regions of a promoter gene operably linked to operation sites, able to specifically bind a RTF which modulates the transcription of said

promoter in response to a gaseous compound, including a genus of a *A. nidulans* P_{alcA} gene able to exhibit AlcR-mediated transactivations induced by acetaldehyde.

The specification provides insufficient data to enable claims directed to any *A. nidulans* P_{alcA} promoter gene region as broadly claimed. Thereby, specific issues including the functional limitation of any fragment of a *A. nidulans* P_{alcA} exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde so as to result in acetaldehyde -inducible expression of a target gene have to be examined and considered for patentability regarding the broadly claimed promoter regions of a *A. nidulans* P_{alcA} gene.

In the instant case, the specification teaches at page 5, the *Aspergillus nidulans* AlcR protein, which binds to the corresponding operator sequence as disclosed in GenBank accession No. S47331, nucleotides 30-308, in response to acetaldehyde (GenBank Accession No. S47331). The specification exemplifies the construction of plasmid pWW192 comprising a PCR-amplified promoter using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3') as primers, from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector. Moreover, the specification teaches transfection of CHO-K1 cells with plasmid pWW192 and induction of gene reporter activity in a dose-dependent manner with increasing concentrations of acetaldehyde from tobacco smoke (p. 8, paragraphs [043]-[046]. Though the specification contemplates other promoters domains containing specific operator sites derived from those found in the A. nidulans P_{alcA} promoter containing modified nucleotides (p. 5, paragraph [027]) that activated by *A. nidulans*-induced AlcR transcription factor, there is no structure/function relationship taught at all for claimed genus of promoter regions of a *A. nidulans* P_{alcA} gene, much less fragments of

any promoter gene. There is no teaching of how many nucleotides may be mutated and/or deleted in the PCR-amplified promoter from a P_{AlcA} containing vector that may affect AlcR-mediated transactivation in the presence of acetaldehyde. Moreover, Applicant has provided little or no guidance beyond the cloning of the PCR-amplified promoter from a P_{AlcA} promoter 5' of a minimal version of the human CMV immediate early promoter containing vector, to enable one of ordinary skill in the art to determine, without undue experimentation, positions of the *A. nidulans* P_{alcA} gene which are tolerant to changes (e.g. by nucleotide substitutions or deletions), and the nature and extent of changes that can be made in these positions to retain the promoter activity under acetaldehyde -induced transactivation by *A. nidulans*-induced AlcR transcription factor.

At the time the invention was made, it was well known in the art that patterns of single mutations in promoters are critical to their structure/function relationship, particularly, various sites or regions directly involved in promoter response elements, TAT elements and initiator elements necessary for binding of trans-activators and RNA polymerase, which regulates transcriptional activation (Romanos et al., 1992, Yeast, pp. 423-488; p. 431, col. 2). The skilled artisan understands that one nucleotide change in a DNA molecule could result in the loss of its biological activity as demonstrated, for example, in the yeast his3 promoter region wherein individual mutations of the regulatory TATA elements, TATAAA, abrogate the functional activity of the promoter, likely by preventing binding of sequence specific DNA-binding proteins (Chen et al., 1988, Proc Natl Acad Sci pp. 2691–2695, Abstract). Since, the relationship between the a *A. nidulans* P_{alcA} gene and transcriptional factors modulating its activity is not well understood and is not predictable, the disclosure provided is not deemed to be descriptive of the

complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision a genus of promoters domains of *A. nidulans* P_{alcA} gene transactivated by the A. *nidulans* AlcR responsive transcription factor. Thus, it is not possible from reading the examples to envision what types of mutations have been introduced, how many mutations have been introduced in each promoter region of the *A. nidulans* P_{alcA} gene so as to exhibit *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde. Though the PCR-amplified promoter from a *A. nidulans* P_{AlcA} using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') as primers and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3'), is identified in the specification, this may not be sufficient, as the ordinary artisan would immediately recognize that active or binding sites in the promoter are affected by mutations within the promoter sequence and upstream promoter elements and other transcription regulatory elements including sequence length and sequence G+C rich content and others. Because the specification is silent about critical residues in *A. nidulans* AlcR-DNA binding activity, let alone critical residues in any responsive factor –DNA binding activity, any substitution (e.g., mutations, deletions) of nucleotide residues can often destroy the activity of the DNA promoter or prevent the *A. nidulans* $P_{AlcA\ gene}$ from exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde.

Since it would require undue experimentation to identify other promoter regions of a *A. nidulans* $P_{AlcA\ gene}$, other than the PCR-amplified promoter from a *A. nidulans* P_{AlcA} using oligonucleotides OWW58 (5'-gatcgacgtcggagctaccatccaataaccc-3') and OWW59 (5'-gatccctgcaggcccgctcgtttgtggctct-3', said fragment cloned into plasmid pWW192, it certainty would require undue experimentation to make and use the invention as claimed. Neither prior art

of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of unidentified *A. nidulans* P_{AlcA} promoters domains, much less an undefined genus of fragments from any promoter gene, able to exhibit responsive transcription factor-mediated transactivation in the presence of any compound being gaseous. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant invention to identify an enormous number of mammalian cells as broadly or generically claimed, with a resultant identification of a promoter regions of a *A. nidulans* P_{AlcA} gene specifically exhibiting *A. nidulans* AlcR-mediated transactivation in the presence of acetaldehyde in a mammalian cell as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The specification does not teach a close definition of the phrase " operator-containing promoters" but discloses at p.4, paragraph [023] structural limitations of said operator sequences which "may comprise a naturally occurring polynucleotide sequence or a polynucleotide sequence derived from a naturally occurring polynucleotide sequence, which can be bound by an

responsive transcription factor (RTF) either constitutively or in an regulating compound (RC)-dependent way.

Claims 1, 2, 4 and 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Berlin et al. (US Patent 6,509,152, Date of Issue Jan. 21, 2003).

Berlin et al. discloses mammalian host cells comprising a chimeric gene encoding a first protein comprising a rapamycin-binding domain (e.g., a responsive transcription factor), and a second chimeric gene encoding a second protein comprising a domain which binds to an FK506-binding protein complex, wherein one of the first or second proteins contains a DNA-binding domain and the other protein comprises a transcriptional activation domain, and a reporter gene, the transcription of which is induced by the presence of rapamycin, wherein said reporter gene is operably linked to a transcriptional regularly site which binds to said DNA binding domain. Clearly, Berlin et al. teaches that the reporter gene is under the control of a promoter which comprises a response element site binding to the DNA binding domain of the first protein comprising a rapamycin-binding domain. Further, Berlin et al. discloses addition of rapamycin in the culture media increase reporter activity (col. 54, lines 31-34; col. 53, lines 9-20, and claim 1).

Thus by teaching all the claims limitations, Berlin et al., anticipate the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 drawn to a mammalian cell does the conjunction "and/or" after subpart a. Therefore claim 1 has been interpreted as comprising both a. and b. and not in the alternative.

Claims 1, 2, 4-7 and 9 are rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record)

Caddick et al., discloses a chemically-inducible plant gene expression cassette comprising a first promoter operatively linked to a regulator sequence which encodes a regulator protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer (current claim 1, subpart a.) and an inducible promoter operatively linked to a target gene, the inducible promoter being activated by the regulator protein (current claim 1, subpart b.; current claim 2) whereby application of the inducer causes expression of the target gene (col. 4, lines 22-29). Moreover, Caddick et al., teaches that the alcA gene promoter (i.e. the alcA gene encodes alcohol dehydrogenase I) is an inducible promoter, activated by the alcR regulator protein (e.g., responsive transcription factor) in the presence of inducer, i.e. by the protein/alcohol or protein/ketone combination (col. 2, lines 65-67 bridging to col. 3, lines 1-4). The alcA/alcR gene

activation system (e.g., alcR gene encoding the alcR regulator protein) is from the fungus *Aspergillus nidulans* (current claims 4, 5, 6 and 7). Moreover, Caddick et al., exemplifies the transient transfection of Maize protoplasts from Black Mexican Sweet cells with the gene expression cassette wherein the alcR gene product is induced by ethanol in the incubating culture media (Example 4, and col. 14 lines 35-36) and stably transformed tobacco plants wherein the alcR gene product is induced by exogenous treatment with cyclohexanone (Example 5; col. 18, lines 55-58) (current claim 9). Further, Caddick et al., teaches that increase in induction of the system is dependent on higher level of expression of alcR (col. 15, lines 10-20)

Caddick et al., do no specifically teach transfection of mammalian cells.

However, at the time the invention was made, White MRH explicitly teaches the use of mammalian host cells to be transfected with an expression vector encoding the *Aspergillus nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters containing specific operator sites from *A. nidulans alcA* promoter. Moreover, White MRH discloses that vectors are introduced in mammalian cells and assay for luciferase reporter gene expression in the presence and absence of ethanol.

Therefore in view of the benefits of using the ethanol-inducible *alc* gene expression system (e.g., time point of induction, expression level, duration of expression) in a variety of plants, as taught by Caddick et al., it would have been *prima facie* obvious for one of ordinary skill in the art to use mammalian host cells to study the ethanol-induce *alc* gene expression system, particularly because White MRH suggest transfecting mammalian cells with expression vectors expressing the *A. nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters the *A. nidulans alcA* promoter. The manipulation

of previously identified DNA reporter genes and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in a transforming a mammalian cell comprising a first promoter operatively linked to a regulator sequence which encodes a regulator protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer, e.g., liquid or gas and an inducible promoter operatively linked to a target gene, the inducible promoter being activated by the regulator protein because Caddick et al., actually exemplifies said system in a variety of plant cells and White MRH teaches the use of said system to transform mammalian host cells in regulated gene expression experiments.

Claims 1 and 3 are rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record) as applied to claims 1, 2, 5-7 and 9 above, and further in view of Flipphi et al., (Bichem. J. 2002, pp. 25-31, of record).

The teachings of Caddick et al., and White are outlined in the paragraph above.

Caddick et al. and White do not specifically teach induction of the alcR gene product in response to compounds being gaseous at the cultivation temperature.

However, at the time the invention was made, Flipphi et al., teaches that acetaldehyde is the sole physiological inducer of ethanol catabolism in *Aspergillus nidulans* (p. 28, col. 2 last paragraph bridging to p. 29, col. 1 first paragraph). Moreover, Flipphi et al., discloses induction of the *alc* genes by acetaldehyde at low external concentrations. Indeed, Flipphi et al., states "even at an external concentration of 32μm, this highly volatile compound could induce the

expression of *alcA*" (p. 28, col. 1, first paragraph), implicitly indicating that acetaldehyde is a gas at culture temperature of 37C (p. 26, col. 1, paragraph 2). Additionally, Flipphi et al., teaches that acetaldehyde is toxic at high concentrations reflected by general transcription decrease (p. 28, col. 1, paragraph 2). (Current claim 3).

Therefore in view of the benefits of using the ethanol-inducible *alc* gene expression system (e.g., time point of induction, expression level, duration of expression) in a variety of plants, as taught by Caddick et al., it would have been *prima facie* obvious for one of ordinary skill in the art to use mammalian host cells to study the ethanol-induce *alc* gene expression system, particularly because White MRH suggest transfecting mammalian cells with expression vectors expressing the *A. nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters the A. nidulans *alcA* promoter. Additionally, it would have been *prima facie* obvious for one of ordinary skill in the art to induce the alcR gene encoding the regulator protein alcR by incubating the host cells under culture conditions comprising non-toxic highly volatile acetaldehyde concentrations, particularly Flipphi et al., exemplifies that acetaldehyde arising from ethanol catabolism at low concentration is the sole inductor of the alc genes. The manipulation of previously identified DNA reporter genes and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in transforming a mammalian cell comprising a first promoter operatively linked to a regulator sequence which encodes a regulator protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer, e.g., liquid or gas and an inducible promoter operatively linked to a target gene, the inducible promoter being activated by the regulator protein because Caddick et al.,

actually exemplifies said system in a variety of plant cells and White MRH teaches the use of said system in transformed mammalian host cells in regulated gene expression experiments.

Claims 1 and 8 are rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record) as applied to claims 1, 2, 5-7 and 9 above, and further in view of Smits et al., (2001, Plasmid, pp. 16-24, of record).

The teachings of Caddick et al., and White are outlined in the paragraph above.

Caddick et al. and White do not specifically teach induction of the alcR gene product in response to compounds being gaseous at the cultivation temperature.

However, at the time the invention was made, Smits et al., teaches expression of heterologous genes in *E. coli* and *Pseudomonas putida* under the control of the *P. putida* GPo1alkB promoter, said promoter being induced by the *P. putida* regulator AlkS which is activated by alkenes, haloalkanes, ethylacetate, ethylether and dicyclopropylketone (p. 16, col. 2, paragraphs 1 and 2). Additionally, Smits et al., exemplifies expression vectors under the control of the construction *P. putida* GPo1alkB promoter useful for expression of an heterologous gene and tested for expression of the reporter gene catechol-2,3-dioxygenase (XylE) in *E. coli* and *P. putida* (p. 17, col. 2, paragraph 1 and Tables 1 and 2). (Current claim 8).

Therefore in view of the benefits of using the ethanol-inducible *alc* gene expression system (e.g., time point of induction, expression level, duration of expression) in a variety of plants, as taught by Caddick et al., it would have been *prima facie* obvious for one of ordinary

skill in the art to use mammalian host cells to study the ethanol-induce *alc* gene expression system, particularly because White MRH suggest transfecting mammalian cells with expression vectors expressing the *A. nidulans*-derived AlcR transcription factor, which in the presence of ethanol activates transcription from promoters the A. nidulans *alcA* promoter. Additionally, it would have been *prima facie* obvious for one of ordinary skill in the art to express a gene in a host cell under the control of the *P. putida* GPo1alkB promoter which is induced by the *P. putida* regulator AlkS (e.g., a response transcription factor), particularly because Smits et al., successfully exemplifies inducible AlkS gene expression in E. *coli* and *P. putida.* The manipulation of previously identified DNA reporter genes and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in transforming a mammalian cell comprising a first promoter operatively linked to a regulator sequence which encodes a regulator protein (e.g., responsive transcription factor) in the presence of an effective exogenous inducer, e.g., liquid or gas and an inducible promoter operatively linked to a target gene, the inducible promoter being activated by the regulator protein because Caddick et al., actually exemplifies said system in a variety of plant cells and White MRH teaches the use of said system in transformed mammalian host cells in regulated gene expression experiments.

Conclusion

Claims 1-9 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

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